ABSTRACT

We currently advocate the concept that non-infectious rhinitis and asthma should be regarded as one syndrome with manifestations in both the nasal and the lower airways. Therefore, management of these conditions should consider targeting both sites of the respiratory tract. Although the pathophysiology of allergic rhinitis and asthma is almost identical when the immunologic and inflammatory aspects are considered, tissue differences render some of the humoral mediators of the allergic reaction more important in one or the other part of the respiratory tract. In accordance to this concept, antihistamines are more effective in rhinitis and have little, if any, effect in asthma, whereas leukotriene receptor antagonists seem to have stronger effects in asthma. Also, beta-adrenergic agonists, which act as smooth muscle relaxants, have only a role in asthma, whereas alpha agonists, which act as vasoconstrictors, only in rhinitis. In this brief review article, we summarize current management strategies in rhinitis and asthma viewed as one condition. In discussing these strategies, we will refer to a number of presentations and discussions that took place at the 2003 meeting of the World Allergy Organization in Vancouver, Canada that were selected for coverage in this Advanced Studies in Medicine issue. (Adv Stud Med. 2004;4(7A):S513-S516)

RHINITIS AND ASTHMA: THE CONCEPT OF A CHRONIC INFLAMMATORY AIRWAY SYNDROME INVOLVING LOCAL AND SYSTEMIC COMPONENTS

It has now become quite clear that, at least in the case of allergic rhinitis and asthma, the entire airways are diseased. Patients with allergic or even nonallergic chronic inflammatory rhinitis, who have no clinical evidence of asthma, show lower airway inflammation, as well as functional lower airway abnormalities, ranging from bronchial hyperresponsiveness to early airway closure, as documented by increased ratio of residual volume to total lung capacity. On the other hand, the prevalence of symptoms of rhinitis in patients with asthma exceeds 85% and even those few asthmatics with no nasal complaints show inflammation in their nasal mucosa. Notably, in individuals with asthma and rhinitis, the severity of the nasal airways component tracks in parallel with that of the lower airways. These observations support the notion that rhinitis and asthma are elements of a single inflammatory syndrome that affects the entire airway tract. We advocate that rhinitis and asthma should be managed as a single entity.

At this point, when only rhinitis is present, there is no evidence that any form of intervention towards lower airway disease is justified, although, in the future, if we identify lower airway abnormalities that constitute risk factors for developing asthma, they may need to be managed. From a recent, prospective study, it has become clear that, at least in adults, not only is rhinitis a risk factor for the development of asthma, but that the risk for asthma increases with increased severity of the upper airway disease. On the basis of current knowledge, vigorous treatment of rhinitis, as well as vigilance for lower airway disease in patients with rhinitis and no asthma are justifiable strategies.

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In patients with rhinitis and asthma, ie, with the chronic inflammatory airway syndrome manifested in its entirety, there is evidence that appropriate management of rhinitis may benefit asthma. This hypothesis has been tested in several studies, in the majority of which the results were supportive. In 2 recently published retrospective analyses, patients with International Classification of Diseases codes for asthma and rhinitis who received treatment for their upper airway condition had reduced numbers of asthma-related hospitalizations and emergency department visits, compared with those who did not receive rhinitis treatment.6,7 In explaining the impact of rhinitis on asthma, one should note that allergic reactions induced in the nose can alter lower airway function and can induce lower airway inflammation.8 The mechanism(s) of the vertical interaction between the nasal and the lower airways are not known, although several hypotheses have been proposed.1 The currently most attractive hypothesis is that of inflammation propagating systemically from the upper to the lower airways, with the participation of elements of the innate and the adaptive immune system.9 This underlines the concept that pharmacological management of the chronic inflammatory airway syndrome may frequently require an agent that targets the systemic inflammatory component. Ideally, systemic steroids could play this role, but their safety profile precludes their use in this context.

**OPTIMAL USAGE OF ANTIHISTAMINES AND LEUKOTRIENE RECEPTOR ANTAGONISTS**

In patients with chronic allergic airway syndrome, it is pertinent to take into account basic information derived from many years of research. First, the elementary allergic reaction (immunoglobulin E-mediated immediate hypersensitivity) involves the release of histamine and sulfidopeptide leukotrienes (peptide leukotrienes, or simply, leukotrienes) upon mast cell and basophil activation. Other allergic mediators are probably also released but their significance is less appreciated given the fact that no specific antagonists exist. Second, histamine and leukotrienes act on target tissues through distinct receptors, but share several biologic properties such as airway smooth muscle constriction, induction of vascular permeability, and vasodilation. They also have some distinct properties; for example, direct activation of neural reflexes, at least in the nasal airways, is a function of histamine, but not of leukotrienes. Among the shared properties, differences in relative potency should be noted, the most evident being the at least 1000-fold stronger contractile effect of leukotrienes on the human airway smooth muscle.10 Third, evidence has accumulated that histamine and leukotrienes are not just molecules with effect tor functions on target tissues such as the smooth muscle, but that they play a role in immune functions and in inflammatory events. Several reports have indicated that histamine activates immune cells including lymphocytes, dendritic cells, and macrophages. For example, as discussed by Dr Marone (page S495), histamine induces release of beta-glucuronidase, a potent lysosomal enzyme, from human lung macrophages and this effect is blocked by a H1-receptor antagonist. The stimulatory effects of leukotrienes on various immune cells have recently started being unveiled. It is now clear, for example, that leukotrienes have multiple effects on the biology of eosinophils, from induction of maturation to prolongation of eosinophil survival.11

Given the multiplicity of the biologic effects, the complementarity and, perhaps, the synergy between histamine and leukotrienes, it is reasonable to raise the possibility that antagonists to these mediators will show impressive strength, when utilized together. Such strength may also derive from the fact that the therapeutic effects of these agents cover the entire allergic respiratory syndrome, as opposed to targeting a single component. Indeed, leukotriene receptor antagonists now have indications for both asthma and allergic rhinitis. A study by Keith et al, summarized on page S529, also proposes that they may be effective in nasal polyposis. In another study, Price and colleagues reported at the World Allergy Organization meeting that a leukotriene receptor antagonist added to an inhaled glucocorticosteroid was superior to doubling the dose of the steroid in the subgroup of asthma subjects who also had a physician diagnosis of rhinitis (see page S527). Antihistamines are successfully used in allergic rhinitis, but studies in asthma have not been, in general, positive.12 The potential role of antihistamines in asthma is discussed in more detail in the summary of the presentation of Dr Wilson at the World Allergy Organization meeting (see page S517), that we have included in this issue. In 1997, Roquet and colleagues published their findings of a study where they combined a leukotriene receptor antagonist and an antihistamine in order to inhibit the early and the late phase of an allergen inhalation challenge in subjects with allergic
asthma. Their results were quite impressive and offered evidence of additive effect. More recently, a study has suggested that, in mild asthma, combination treatment with an antihistamine and a leukotriene receptor antagonist may be equally effective as the combination of a nasal and an inhaled glucocorticosteroid. It should be noted that a leukotriene receptor antagonist alone is generally inferior to a low-moderate dose of an inhaled glucocorticosteroid in mild to moderate asthma. There is quite some controversy as to whether the combination of an antihistamine with a leukotriene receptor antagonist is as potent as a nasal steroid in the treatment of allergic rhinitis. A couple of recent studies have indicated that this may, indeed, be the case, while a couple of others have found the nasal steroid to be more effective. On the basis of the above, our utilization of combination treatment with an antihistamine and a leukotriene receptor antagonist should be considered as an alternative management approach (instead of a nasal and an inhaled steroid) in patients with the mild persistent form of the chronic allergic airway syndrome and the choice may be left to the patient, in an effort to improve the adherence factor. In moderate to severe disease, the role of topical glucocorticosteroids is pertinent and there is no evidence at this point that an antihistamine/leukotriene receptor antagonist combination will be as effective.

**Optimal Usage of Topical Glucocorticosteroids**

Topical glucocorticosteroids remain the most effective form of treatment in chronic inflammatory airway syndrome. In those patients with full manifestation of the syndrome, to achieve maximum effectiveness, topical steroids need to be used in the nasal and the lower airways simultaneously. In patients with persistent rhinitis but with mild intermittent asthma, several studies have indicated that the use of nasal steroids benefits the function of the lower airways. Yet, a few other studies have failed to detect such beneficial effect.

Like all treatment options, topical steroids have their limitations. In the nasal airways, for example, 20% of patients obtain no relief. In the lower airways, the dose response to inhaled steroids is relatively flat and the dose needs to probably be quadrupled, if one wants to assess the possibility of better effectiveness with increased dose. Most of the time, this will result in a total steroid load in which systemic effects can become evident. Considerable efforts have been made by the pharmaceutical industry to develop glucocorticosteroids with more favorable safety and efficacy profiles and the newest available agents reflect this work. Currently, another inhaled steroid, ciclesonide, is under development; this agent appears to have the safest clinical profile so far, and some of its properties are reviewed by the summary of a presentation by Dr Kaliner at the World Allergy Organization meeting (see page S520). Although topical steroids have a wide spectrum of anti-inflammatory activity that covers the majority of pathologic elements identified in the chronic inflammatory airway syndrome, some aspects of inflammation and, most importantly, some aspects of altered physiology, may not be responsive to steroid treatment. For example, there have been questions as to whether, at least in the lower airways, inhaled steroids can suppress leukotriene production, since they do not appear to inhibit mast cell activation. Also, some of the functional airway abnormalities that have now well been demonstrated in asthma are unaffected by inhaled steroid treatment. The latter problem may derive from the fact that there is no convincing evidence that steroids can reverse structural airway abnormalities that are operative in this syndrome (airway remodeling).

Given the above limitations, one should consider the use of topical steroids together with an agent that provides direct symptom relief. In allergic rhinitis, there is little evidence that the addition of an antihistamine or a leukotriene receptor antagonist improves clinical outcomes, although well-designed studies targeting this question have not been performed. In the lower airways, the addition of an agent that has airway smooth muscle-relaxing effects to an inhaled steroid has been proven a better option in managing moderate or severe persistent asthma, compared to doubling or even quadrupling the inhaled steroid dose. That second agent can be a long-acting beta-adrenergic agonist, a leukotriene receptor antagonist, or even low-dose theophylline. In mild persistent asthma, there is little justification for the use of a second controller, in addition to an inhaled steroid or to a leukotriene receptor antagonist. In moderate asthma, the addition of a long-acting beta-adrenergic agonist to a fixed dose of an inhaled steroid has been more effective than the addition of a leukotriene receptor antagonist. Also, the ability to combine the inhaled steroid with the long-acting beta-agonist in a single inhalation device has made this approach very practical and has
improved patient adherence. Yet, it should be noted that there may be patients whose lung function deteriorates when treated with beta2-adrenergic agonists.\textsuperscript{21,22} These are primarily individuals with the Arg/Arg polymorphism at position 16 of the beta2-adrenergic receptor. Approximately 25% of African Americans and around 13% of European Americans express this genotype. Currently, only one product combining the long-acting beta-agonist salmeterol with the steroid fluticasone is available in the United States. Another product combining formoterol and budesonide is already in use in several countries and is under evaluation in the United States. This product may have the advantage that it could be used in adjustable dosing schemes. One Canadian and one European study exploring this possibility in the context of managing asthma exacerbations were presented at the World Allergy Organization meeting and are summarized in this issue.

REFERENCES